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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		Attorney's Docket Number 06267.0053 U.S. Application No. 09/673794
International Application. No. PCT/FI99/00329	International Filing Date April 23, 1999	Priority Date Claimed April 23, 1998

Title of Invention: CONTROLLED RELEASE PERORAL COMPOSITIONS OF LEVOSIMENDAN

Applicants For DO/EO/US: 1) Ilkka LARMA, 2) Maarit HARJULA, 3) Saila ANTILA, and 4) Lasse LEHTONEN

Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:
    a. [ ] Verified Small Entity Statement.
    b. [ ] Copy of Notification of Missing Requirements.
    c. [X] Copy of Cover Page of WIPO Publication including an Abstract (1 sheet).

U.S. APPLICATION NO.	INTERNATIONAL APPLICATION NO.	ATTORNEY DOCKET NUMBER
09/673794	PCT/FI99/00329	06267.0053

17. [X] The following fees are submitted: | CALCULATIONS

Basic National Fee (37 CFR 1.492(a)(1)-(5)):

Search Report has been prepared by the EPO or JPO.....$860.00 | $860

International preliminary examination fee paid to USPTO (37 CFR 1.482).....$690.00

No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$760.00

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$1,000.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4).....$ 100.00

ENTER APPROPRIATE BASIC FEE AMOUNT = | $860.00

Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)). | $

Claims	Number Filed	Number Extra	Rate	
Total Claims	17 -20=	0	X $18.00	$
Independent Claims	3 - 3=	0	X $80.00	$
Multiple dependent claim(s) (if applicable)			+$270.00	$

TOTAL OF ABOVE CALCULATIONS = | $860.00

Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28) | $

SUBTOTAL = | $860.00

Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). + | $

TOTAL NATIONAL FEE = | $860.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property + | $

TOTAL FEES ENCLOSED = | $860.00

Amount to be refunded | $

charged | $

a. [X] A check in the amount of **$860.00** to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-0916. A duplicate copy of this sheet is enclosed.

The Commissioner is hereby authorized to charge any other fees due under 37 C.F.R. §1.16 or §1.17 during the pendency of this application to our Deposit Account No. 06-0916.

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Submitted: October 20, 2000

PATENT

Attorney Docket No.: 06267.0053

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Ilkka LARMA et al.	)	
	)	
Serial No.: Unassigned	)	Group Art Unit: Unassigned
	)	
Filed: Filed Herewith	)	Examiner: Unassigned

For: CONTROLLED RELEASE PERORAL COMPOSITIONS OF LEVOSIMENDAN being a **National Stage filing** of PCT International Application No. PCT/FI99/00329, filed on April 23, 1999

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Preliminary Amendment

Please amend the application as follows:

In the Specification:

Please amend the specification as follows:

Page 1, after the title, insert a first paragraph as follows:

--This application is a national stage filing of PCT International Application No. PCT/FI99/00329, filed on April 23, 1999, which published in English.--

In the Claims:

Please add new claims 11-17 and amend claims 1-4 and 7-10 as follows

1. (Amended) A controlled release composition for oral administration comprising a) a therapeutically effective amount of levosimendan and b) a drug release controlling component for providing the release of levosimendan over an extended period of time and a steady-state plasma level for the levosimendan metabolite (R)-N-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]acetamide [(II)] of less than 20 ng/ml [, preferably less than 10 ng/ml].

2. (Amended) A composition of claim 1, wherein the drug release controlling component allows levosimendan to be released substantially completely before the composition reaches the large intestine of the host to which the composition is to be administered.

3. (Amended) A composition of claim 1, [or 2] wherein the drug release controlling component is hydrophilic gel forming polymer or a vegetable fat or oil or a fatty acid ester.

4. (Amended) A controlled release composition for oral administration comprising a) a therapeutically effective amount of levosimendan and b) a drug release controlling component for providing the release of levosimendan over an extended period of time, wherein the total in vitro dissolution time of the composition, determined according to the USP XXII basket assembly method in phosphate buffer pH 5.8, ranges from about 1 to about 4 [is substantially between 1 and 4] hours for at least 90 percent [per cent] of the content of levosimendan.

7. (Amended) A composition of claim 5, [or 6] wherein the rapid release portion comprises levosimendan and microcrystalline cellulose.

8. (Amended) A composition of claim 6, [or 7] wherein the release controlling hydrophilic gel forming polymer is hydroxypropylmethyl cellulose, alginic acid or a mixture thereof.

9. (Amended) A composition of claim 5, [any of claims 5 - 8] wherein about 25 to about [-] 75% by [, preferably about 30 - 70%, more preferably about 40 - 60% per] weight of levosimendan [the drug] is in the controlled release portion.

10. (Amended) A composition of claim 6, [any of claims 5 - 9] wherein the amount of the hydrophilic gel forming polymer is about 20 to about [-] 80% by [, preferably about 30 - 70%, per] weight of the composition.

--11. A composition of claim 1, wherein the drug release controlling component provides for a steady-state plasma level for the levosimendan metabolite of less than 10 ng/ml.

12. A composition of claim 5, wherein about 30 to about 70% by weight of levosimendan is in the controlled release portion.

13. A composition of claim 5, wherein about 40 to about 60% by weight of levosimendan is in the controlled release portion.

14. A composition of claim 6, wherein the amount of the hydrophilic gel forming polymer is about 30 to about 70% by weight of the composition.

15. A method for the treatment of congestive heart failure, which comprises administering to a host in need of the treatment a composition of claim 1.

16. A method for the treatment of congestive heart failure, which comprises administering to a host in need of the treatment a composition of claim 4.

17. A method for the treatment of congestive heart failure, which comprises administering to a host in need of the treatment a composition of claim 5.--

Remarks

Claims 1-17 are pending in this application. Support for new claims 11-14 appears in original claims 1, 9 and 10. Support for new claims 15-17 appears on page 1, lines 3-7 of the specification.

If there is any fee due in connection with the filing of this Preliminary Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: 
Steven J. Scott
Reg. No. 43,911

Date: October 18, 2000

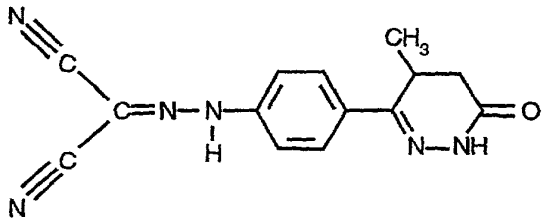
CONTROLLED RELEASE PERORAL COMPOSITIONS OF LEVOSIMENDAN

Technical field

The present invention relates to peroral pharmaceutical compositions which release levosimendan in a controlled fashion with reduced occurrence of undesired effects. Levosimendan, or (-)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile, is useful in the treatment of congestive heart failure.

Background of the invention

Levosimendan, which is the (-)-enantiomer of [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile, and the method for its preparation is described in EP 565546 B1. Levosimendan is potent in the treatment of heart failure and has significant calcium dependent binding to troponin. Levosimendan is represented by the formula:



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The hemodynamic effects of levosimendan in man are described in Sundberg, S. et al., Am. J. Cardiol., 1995; 75: 1061-1066. Pharmacokinetics of levosimendan in man after i.v. and oral dosing is described in Sandell, E.-P. et al., J. Cardiovasc. Pharmacol., 26(Suppl.1), S57-S62, 1995. The use of levosimendan in the treatment of myocardial ischemia is described in WO 93/21921. Clinical studies have confirmed the beneficial effects of levosimendan in heart failure patients.

Oral administration of levosimendan has proved to be difficult, especially when the aim is a therapeutical effect over an extended period of time. Firstly, the elimination half-life of levosimendan in human is short, about 1 h. Therefore, using conventional immediate release oral formulations levosimendan should be administered frequently during the day. Secondly, the gastrointestinal absorption of levosimendan is rapid. Therefore, using immediate release oral formulations high peak plasma concentrations of levosimendan are reached rapidly and abruptly, typically within 1 hour. High plasma

concentrations of levosimendan tend to increase heart rate which is an undesired effect in heart failure patients.

Long-acting peroral compositions provide many advantages over conventional peroral rapid release compositions. Such advantages include smaller variation of drug concentrations in plasma and, as a result, steady therapeutic response, reduced frequency of administration and reduction of side effects. Typically long-acting compositions are prepared by mixing the drug, a release controlling agent and possible excipients, and pressing the mixture into matrix tablets. Typical long-acting compositions release drug in the upper as well as in the lower gastrointestinal tract.

Attempts to administer levosimendan in conventional long-acting preparations have been disappointing. Undesired effects such as severe headache, palpitation and increased heart rate are frequently observed when levosimendan is administered in long-acting preparations which are conventionally used in the art to obtain a therapeutical effect over an extended period of time. Therefore there is a need for new methods and compositions for administering levosimendan orally, in particular for methods and compositions which provide a therapeutical effect of levosimendan over an extended period of time and which avoid the drawbacks associated with the conventional long-acting preparations of levosimendan.

Summary of the invention

It has been found that levosimendan is susceptible to metabolization in the lower gastrointestinal tract, in particular in the large intestine, by the intestinal bacteria. Such metabolic route results ultimately in the formation of an active first-pass metabolite, (R)-N-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]acetamide (II) having elimination half-life substantially longer than that of levosimendan. The accumulation of the active metabolite has been found to be the cause of the undesired effects associated with the long-acting levosimendan preparations. The discovery of the active metabolite and its formation route makes it now possible to design controlled release preparations which show a reduced occurrence of undesired effects and which are well suited for the treatment of heart failure patients.

Therefore the object of the present invention is to provide peroral compositions, in particular compositions which provide a therapeutical effect over an extended period of time, from which levosimendan is released steadily and, preferably, substantially completely before it reaches the lower part of the gastrointestinal tract, particularly the large intestine, so that the formation of the active metabolite remains at low level.

Thereby, the concentration of the active metabolite in the plasma of the patient remains at sufficiently low level so that the undesired effects caused by the accumulation of the active metabolite are avoided while a therapeutical effect over an extended period of time is obtained.

Brief description of the drawings

Fig. 1 shows a calibration sample for the active metabolite (II) from a volunteer as determined by liquid chromatography-tandem mass spectrometry.

Fig. 2 shows a post-dose plasma sample for the active metabolite (II) from a volunteer as determined by liquid chromatography-tandem mass spectrometry.

Fig. 3 shows in vitro dissolution curve for formulation 1 of Example 1 in phosphate buffer pH 5.8.

Fig. 4 shows in vitro dissolution curve for formulation 2 of Example 1 in phosphate buffer pH 5.8.

Fig. 5 shows in vitro dissolution curve for formulation 3 of Example 1 in phosphate buffer pH 5.8.

Fig. 6 shows in vitro dissolution curve for the reference formulation of Example 3 in phosphate buffer pH 5.8.

Detailed description

The present invention provides an improved oral delivery system for levosimendan compared to conventional immediate release and long-acting preparations. The advantages include:
- lower peak plasma levels of levosimendan which hence reduce the occurrence of the undesired effects of high levosimendan levels such as increased heart rate,
- reduced frequency of administration, and
- reduced accumulation of the active metabolite (II) which mean higher tolerability of the drug, i.e. less undesired effects caused by the active metabolite, such as severe headache, palpitation and increased heart rate.

The plasma level of metabolite (II) correlates well with the occurrence of undesired effects such as severe headache, palpitation and increased heart rate. In the

optimal levosimendan treatment of heart failure patients the steady-state plasma level of metabolite (II) should be less than 20 ng/ml, preferably less than 10 ng/ml.

The advantages are provided according to the invention by a controlled release composition comprising a) a therapeutically effective amount of levosimendan and b) a drug release controlling component for providing the release of levosimendan in a patient over an extended period of time and a steady-state plasma level for metabolite (II) of less than 20 ng/ml, preferably less than 10 ng/ml.

The term "an extended period of time" means above at least one hour, preferably at least two hours, after administration. The steady-state plasma level of metabolite (II) as defined above refers to an average among a group of patients.

Preferably the drug release controlling component allow levosimendan to be released substantially completely before the composition reaches the large intestine.

The term "drug release controlling component" relates generally to different technologies that can be applied for controlling and extending the release of levosimendan according to the invention. Such technologies include matrix formulations (e.g. matrix tablets, granules or pellets) or coated formulations (e.g. coated tablets, granules or pellets, or microcapsules). The drug release controlling components such as coating and matrix materials, and the methods for the preparation of matrix and coated formulations are well know in the art. The choice of the materials and the amounts used depends on the desired release pattern and is routine to one skilled in the art. Any release controlling materials, e.g. matrix or coating materials, or their combinations which are suitable for obtaining the release pattern of the invention can be used as a drug release controlling component. Typical release controlling components useful in the invention include, but are not limited to, hydrophilic gel forming polymers such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethyl celluloses, alginic acid or a mixture thereof; vegetable fats and oils including vegetable solid oils such as hydrogenated soybean oil, hardened castor oil or castor seed oil (sold under trade name Cutina HR), cotton seed oil (sold under the trade names Sterotex or Lubritab) or a mixture thereof; fatty acid esters such as triglycerides of saturated fatty acids or their mixtures e.g. glyceryl tristearates, glyceryl tripalmitates, glyceryl trimyristates, glyceryl tribehenates (sold under the trade name Compritol) and glyceryl palmitostearic acid ester.

According to the invention it is also possible to use formulations which are designed to have extended residence time in the upper gastrointestinal tract, e.g. the

stomach. This reduces the risk of levosimendan metabolization in the large intestine and the subsequent formation of the active metabolite (II). Such compositions, e.g. floating or buoyant formulations, have the advantage that the total release time of the drug can be designed to be substantially longer, since it takes substantially longer time before the composition reaches the lower part of the gastrointestinal tract. Compositions having extended residence time in the stomach are described e.g. in US 4,126,672, US 4,814,178, US 4,777,033, US 5,232,704 and EP 539059.

Thus, any controlled/extended release composition of levosimendan, which gives a steady-state plasma level for metabolite (II) of less than 20 ng/ml, preferably less than 10 ng/ml, can be used according to the present invention.

The steady-state plasma level for metabolite (II) can be measured for any composition by administering the composition of levosimendan to a volunteer or group of volunteers once or several times a day for several days until a steady state level of (II) is reached. The plasma levels of the active metabolite (II) can then be measured according to the procedure described in detail in Example 2.

One aspect of the invention is a controlled release composition of levosimendan for oral administration which is characterized by its in vitro dissolution pattern.

In particular, the invention relates to a controlled release composition for oral administration comprising a) a therapeutically effective amount of levosimendan and b) a drug release controlling component for providing the release of levosimendan over an extended period of time, which composition is able to show a total in vitro dissolution time, determined according to the USP XXII basket assembly method in phosphate buffer pH 5.8 (at 50 or 100 rpm), substantially between 1 and 4 hours, for at least 90 per cent of the content of levosimendan.

More preferably, the composition of the invention shows a total in vitro dissolution time substantially between 1 and 3 hours, for at least 90 per cent of the content of levosimendan.

The drug release controlling component or components can be chosen as described above. Again, typical release controlling components include, but are not limited to, hydrophilic gel forming polymers such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethyl celluloses, alginic acid or a mixture thereof; vegetable fats or oils or fatty acid esters such as hydrogenated soybean oil, hardened castor oil or glyceryl palmitostearate;.

The method of determining the in vitro dissolution pattern of the compositions of the invention is described in Example 3.

The composition of the invention can be e.g. in the form of a tablet, capsule, granulates or powder.

A particularly preferred embodiment of the invention is obtained by combining a rapid release portion comprising levosimendan optionally together with an excipient with a controlled release portion comprising levosimendan and a drug release controlling component. The drug release controlling component can be chosen as described above, but is preferably a hydrophilic gel forming polymer. Particularly preferred is a composition comprising (a) a rapid release portion in the form of a powder comprising levosimendan together with at least one excipient, and (b) a controlled release portion in the form of granulates comprising levosimendan and a release controlling hydrophilic gel forming polymer. The rapid release portion in the form of a powder and the controlled release portion in the form of granulates are preferably in a freely flowing mixture which can be filled in a capsule, such as a gelatine capsule or a HPMC capsule.

The particularly preferred composition of the invention comprises 0.05 - 20 %, preferably 0.1 - 10 %, more preferably 0.2 - 3 %, per weight of the composition, of levosimendan. The drug dose is divided between the rapid release and the controlled release portions. Generally about 25 - 75 %, preferably about 30 - 70 %, more preferably about 40 - 60 % per weight of the drug is in the controlled release portion.

In general, the daily dosage of levosimendan in man in oral administration is from about 0.1 to 20 mg, typically from about 0.5 to 10 mg, in one daily dose or divided into several doses per day. The dosage depends e.g. on the age, body weight and condition of the patient. The composition of the preferred embodiment comprises from about 0.1 to 5 mg, typically from about 0.2 to 2 mg, of levosimendan divided between the rapid release and the controlled release portions. Preferred peak plasma levels of levosimendan in steady state for the treatment of congestive heart failure are within the range of from about 1 to about 100 ng/ml, more preferably from about 5 to about 60 ng/ml, and most preferably from about 10 to about 50 ng/ml.

A suitable excipient in the rapid release portion is a filler such as microcrystalline cellulose or lactose. Microcrystalline cellulose is a preferred excipient and is available in various grades such as Avicel PH101, Avicel PH102 or Avicel PH-200. The amount of the excipients in the rapid release portion is about 20 - 70 %,

preferably about 30 - 60 %, per weight of the composition. A suitable lubricant such as stearic acid or magnesium stearate can be added to the rapid release portion. Stearic acid is the preferred lubricant.

Release controlling hydrophilic gel forming polymers include, but are not limited to hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethyl celluloses, alginic acid or a mixture thereof. Preferred is a mixture of alginic acid with another hydrophilic gel forming polymer, in particular a mixture of alginic acid and hydroxypropylmethyl cellulose. Hydroxypropylmethyl cellulose is commercially available in various types, e.g. Methocel K100 (m.w. 26,000 g/mol), Methocel K4M (m.w. 86,000 g/mol, Methocel K15M (m.w. 120,000 g/mol) and Methocel K100M. The viscosity of these grades in 2 % water solution (20 °C) is 100 cP, 4000 cP, 15000 cP and 100000 cP, respectively. Hydroxypropylmethyl cellulose with viscosity between 50 –2000 cP is preferred. Methocel K100 is the preferred grade of hydroxypropylmethyl cellulose.

A suitable lubricant such as stearic acid or magnesium stearate can be added to the controlled release portion. Stearic acid is the preferred lubricant.

The amount of the hydrophilic gel forming polymer in the particularly preferred embodiment of the invention is about 20 - 80 %, preferably 30 - 70 %, per weight of the composition. Preferably the hydrophilic gel forming polymer is a mixture of alginic acid and hydroxypropylmethyl cellulose. Suitably the amount of alginic acid is from about 10 to 50 %, preferably from about 20 to 40 %, per weight of the total hydrophilic gel forming polymer.

The amount of the rapid release portion is in the particularly preferred embodiment of the invention from about 20 to 80 %, preferably from about 30 to 70 %, more preferably from about 40 to 60 %, per weight of the composition. The amount of the lubricant, if present, is from about 0.3 to10 %, more preferably from about 0.5 to 5 %, per weight of the composition.

Another preferred embodiment of the invention is obtained by mixing the drug release controlling component, levosimendan and excipients e.g. all in powder form, and filling the mixture into a capsule, such as a gelatine capsule or a HPMC capsule. Drug release controlling component can be chosen as described above. Preferably the drug release controlling component is a hydrophilic gel forming polymer, which in this embodiment is used in an amount from about 10 to 70 %, preferably from about 15 to 60 %, most preferably from about 20 to 40 %, per weight of the composition. Release

controlling hydrophilic gel forming polymers include, but are not limited to hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethyl celluloses, alginic acid or a mixture thereof. The most preferred drug release controlling component is hydroxypropylmethyl cellulose, and particularly hydroxypropylmethyl cellulose with viscosity between 50 –2000 cP such as Methocel K100, and alginic acid or a mixture thereof. The amount of excipient (e.g. microcrystalline cellulose or lactose) is suitably used in this embodiment in an amount from about 30 to 90 %, preferably from about 40 to 80 %, most preferably from about 50 to 70 % per weight of the composition. Levosimendan is used in an amount as described for the previous preferred embodiment.

Yet another preferred embodiment of the invention is in a form of a matrix tablet which is obtained by mixing the drug release controlling component, levosimendan and excipients, such as microcrystalline cellulose, lactose and/or stearic acid, and compressing the mixture into matrix tablets with a suitable tablet machine. Again, drug release controlling component can be chosen as described above. Preferably the drug release controlling component is a hydrophilic gel forming polymer or a vegetable fat or oil or a fatty acid ester as defined above. In this embodiment the drug release controlling component is used in an amount from about 0.5 to 60 % per weight of the composition, and the amount of excipient (e.g. microcrystalline cellulose) is suitably used in an amount from about 30 to 99 %, per weight of the composition. If the drug release controlling component is a hydrophilic gel forming polymer, e.g. hydroxypropylmethyl cellulose, and preferably hydroxypropylmethyl cellulose with viscosity between 50 – 2000 cP such as Methocel K100, alginic acid or a mixture thereof, the drug release controlling component is used in an amount from about 5 to 60 %, preferably from about 10 to 50 %, most preferably from about 15 to 40 %, per weight of the composition, and the amount of excipient (e.g. microcrystalline cellulose) is suitably used in an amount from about 30 to 95 %, preferably from about 50 to 90 %, most preferably from about 60 to 85 %, per weight of the composition. If the drug release controlling component is a vegetable fat or oil or a fatty acid ester, e.g. hydrogenated soybean oil, hardened castor oil or glyceryl palmitostearate, the drug release controlling component is used in an amount from about 0.5 to 30 %, preferably from about 2 to 20 %, most preferably from about 3 to 15 %, per weight of the composition, and the amount of excipient (e.g. microcrystalline cellulose) is suitably used in an amount from about 70 to 99 %, preferably from about 80 to 98 %, most preferably from about 85 to 97 %, per weight of the composition. Levosimendan is used in an amount as described for the previous preferred embodiment.

The following examples are meant to further illustrate the invention without limitation.

EXAMPLE 1. Formulation examples.

Formulation 1.

Granule portion:	Levosimendan	1.0 mg
	Alginic acid	18.0 mg
	Methocel K100LV	37.0 mg
	Stearic acid	0.6 mg
Powder portion:	Levosimendan	1.0 mg
	Avicel PH101	84.0 mg
	Stearic acid	1.5 mg

Formulation 2.

Granule portion:	Levosimendan	1.0 mg
	Alginic acid	23.0 mg
	Methocel K100LV	46.0 mg
	Stearic acid	-
Powder portion:	Levosimendan	1.0 mg
	Avicel PH101	69.5 mg
	Stearic acid	1.5 mg

Formulation 3.

Granule portion:	Levosimendan	1.0 mg
	Alginic acid	28.0 mg
	Methocel K100LV	56.0 mg
	Stearic acid	0.9 mg
Powder portion:	Levosimendan	1.0 mg
	Avicel PH101	56.0 mg
	Stearic acid	1.5 mg

Formulation 4.

Granule portion:	Levosimendan	1.0 mg
	Alginic acid	33.0 mg
	Methocel K100LV	66.0 mg
	Stearic acid	0.6 mg
Powder portion:	Levosimendan	1.0 mg
	Avicel PH101	43.0 mg
	Stearic acid	1.5 mg

In the above examples the material for the granule portion was sieved and mixed until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The powder blend was sieved through 0.6 mm screen. The mass was dry

granulated by slugging (compressed using a tabletting machine). In this procedure the mass was compacted using Bepex Pharmapactor L200/50P, compression force approximately 45 kN. The compacted mass was sieved and granules of 0,7 - 1,7 mm were collected.

The material for the powder portion except stearic acid was sieved and mixed until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The granule portion and the powder portion and the stearic acid are mixed until homogenous in a suitable mixer such as Turbula mixer or Zanchetta container mixer. The mass is filled into hard gelatine capsules no 3. In stead of hard gelatine capsules, HPMC capsule shells no. 3 can also be used.

EXAMPLE 2. Determination of the active metabolite (II) in human plasma by liquid chromatography-tandem mass spectrometry

Preparation of calibration samples

The active metabolite (II) is added in 20 µl of phosphate buffer, pH 7.2 to 0.5 ml of analyte-free plasma. The amounts of analyte added are 0.100, 0.250, 0.500, 1.00, 2.50, 3.75, 5.00, 7.50 and 12.5 ng. After being vortexed for 20 seconds and left standing for 10 minutes, the 2500 pg of internal standard (R)-N-[4-(1,4,5,6-tetrahydro-4-ethyl-6-oxo-3-pyridazinyl)phenyl]acetamide is added in 20 µl of phosphate buffer, pH 7.2. The mixture is vortexed for 1 minute and left standing for 15 minutes. The calibration samples are alkalised with 50 µl of 0.1 M sodium hydroxide and vortexed for 20 seconds. The calibration samples are extracted with 5 ml of ethyl acetate:hexane (8:2) by vortexing for 3 minutes. After centrifugation for 7 minutes the organic layer is separated and concentrated at 40 °C using TurboVap evaporator. When the calibration samples are dry, 200 µl of ethyl acetate:hexane (8:2) is added, vortexed for 1 minute and concentrated at 40 °C using TurboVap evaporator. After that 200 µl of methanol-2 mM ammonium acetate (1:1) is added, the calibration samples are vortexed for 1 minute and left standing for 5 minutes. After centrifugation for 7 minutes the supernatant is transferred into an unused conical autosampler vial for liquid chromatographic-tandem mass spectrometric analysis.

Preparation of samples

The samples are processed as described above but the first buffer addition is analyte-free.

Liquid chromatography-tandem mass spectrometry

Analyses are performed using a PE Sciex API 300 tandem quadrupole mass spectrometer equipped with a heated nebulizer interface. A Hewlett-Packard HP1090L system is used for HPLC. The column applied is a LiChrosorb RP-18 reversed phase column (250 x 4 mm ID, 10 µm particles, E. Merck). The mobile phase consists of methanol-2 mM ammonium acetate pH 5, (60:40 v/v). The flow-rate is 1 ml/min. An aliquot of 100 µl of extract is injected into the liquid chromatographic column.

The column eluent is flowed into the mass spectrometer without a split. The discharge needle current is set at 4 kV. Nebulizer gas pressure (nitrogen) of 5 bars is used. The interface heater is set at 500 °C. Orifice plate voltage is 25 V. Positive ions are sampled into the quadrupole mass analyser.

Determinations are carried out by using the selected reaction monitoring technique. The first quadrupole filter of the mass spectrometer, Q1, is set to pass the protonated molecules at m/z 246 for active metabolite (II) and m/z 260 for internal standard for collision-induced fragmentation in Q2. The respective product ions, at m/z 204 and m/z 218, are then allowed to pass Q3 for monitoring. A dwell time of 200 ms and a pause time of 100 ms is used. The selected reaction monitoring chromatograms are recorded using a PE Sciex API 300 Data System.

Quantitation and calculations

Peak area ratios of analyte and its internal standard are plotted against concentrations. Determination of calibration curve equations and concentrations of unknown samples are carried out with the PE Sciex API 300 Data System and the PE Sciex MacQuan 1.4 programme. The limit of quantitation is 0.200 ng/ml. The calibration curve for active metabolite (II) is prepared.

Specificity

The product ions of active metabolite (II) and its internal standard are monitored using the selected reaction monitoring technique. The method is specific regarding the background arising from the plasma. No interfering peaks are observed in blank plasma extracts. Figures 1 and 2 show a calibration plasma sample and a post-dose plasma sample from a volunteer.

EXAMPLE 3. In vitro and in vivo experiments for the compositions of the invention

Formulations 1, 2 and 3 of Example 1 were subjected to a dissolution test. The dissolution rate of the formulations was tested by a method of U.S. Pharmacopoeia XXII (basket assembly method) in phosphate buffer pH 5.8 at 50 rpm. The results for formulations 1, 2 and 3 are shown in Figures 3, 4 and 5, respectively.

Formulations 1, 2 and 3 of Example 1 were then administered to healthy volunteers as a single oral dose of 2 mg levosimendan. Each group consisted of 9 individuals. The plasma level of metabolite (II) was determined 12 hours after administration. The results are shown in Table 1.

TABLE 1. Plasma concentrations (pg/ml) of metabolite (II) in healthy volunteers 12 h after a single oral dose of levosimendan (n=9). Clinical study 3001047.

Subject	Formulation 1	Formulation 2	Formulation 3
1	<	<	<
2	<	205	<
3	298	295	347
4	214	240	262
5	<	<	<
6	249	572	1300
7	<	<	<
8	<	<	<
9	<	392	<
MEAN	85	189	212
SD	129	208	429

SD=standard deviation

< = under determination limit (200 pg/ml)

EXAMPLE 4. In vitro and in vivo experiments for the reference composition.

A reference formulation consisting of

Levosimendan	2.0 mg
Methocel K4M	35.0 mg
Avicel PH101	101.6 mg
Stearic acid	1.4 mg

was subjected to a dissolution test. The formulation was prepared by sieving and mixing the powdery material until homogenous and filling the mass into hard gelatine capsules no 3.

The dissolution rate of the formulations was tested by a method of U.S. Pharmacopoeia XXII (basket assembly method) in phosphate buffer pH 5.8 at 100 rpm. The results are shown in Figure 6.

The reference formulation was then administered to 8 healthy volunteers as a single oral dose of 2 mg levosimendan. The plasma level of metabolite (II) was determined 12 hours after administration. The results are shown in Table 2.

TABLE 2. Plasma concentration (pg/ml) of metabolite (II) in healthy volunteers 12 h after a single oral dose of levosimendan (n=8). Clinical study 3001047.

Subject	Ref. Formulation
1	<
2	283
3	1330
4	1260
5	253
6	268
7	492
8	833
MEAN	590
SD	496

SD=standard deviation

< = under determination limit (200 pg/ml)

Thus, the formulations of the invention having the total in vitro dissolution time as determined according to the USP XXII basket assembly method in phosphate buffer pH 5.8 substantially between 1 and 4 hours for at least 90 per cent of the content of levosimendan give significantly lower plasma level of metabolite (II) in vivo than the reference formulation which have slower dissolution rate.

EXAMPLE 5. Plasma levels of levosimendan and the active metabolite (II) after 7 days levosimendan administration

In a steady-state clinical study 1 mg of levosimendan was administered orally to healthy volunteers three times a day for 7 days. The plasma levels of levosimendan and metabolite (II) were followed during the treatment. The formulation used was as Formulation 3 of Example 1 except that the total amount of levosimendan was 1 mg and of microcrystalline cellulose (Avicel PH-200) 51.0 mg. The mean plasma levels of levosimendan 1 and 4 hours after the last dose (day 7) and of metabolite (II) 8 hours after the last dose (day 7) are shown in Table 3.

TABLE 3. Mean plasma levels of levosimendan and the active metabolite (II) after 7 days levosimendan administration.

	Levosimendan (day 7)		Metabolite (II) (day 7)
	1 h	4 h	8 h
Plasma level	15.4	8.9	3.44
SD (ng/ml)	8.9	4.9	1.84
N	14	14	13

SD = standard deviation
N = number of individuals

The results show that the formulation of the invention provides steady and therapeutically effective plasma levels of levosimendan over an extended period of time while the steady-state plasma levels of metabolite (II) remain at acceptable levels.

EXAMPLE 6. Further formulation examples.

Formulation 6 (capsule)

Levosimendan	1,0 mg
Methocel K 100 LV	35,0 mg
Avicel PH-200	80,5 mg
Stearic acid	6,4 mg

Levosimendan, Methocel K 100 LV and Microcrystalline cellulose (Avicel) were sieved and mixed in a suitable mixer (Turbula or equivalent). Stearic acid was then sieved and mixed with the mass in a suitable mixer (Turbula or equivalent). The

mass was then filled into white gelatine capsule shells no 3 using capsule filling machine Harro Höfliger, MG2 or equivalent.

Dissolution data for the above formulation (USP XXII, phosphate buffer, pH 5.8, 100 rpm) is shown in Table 4:

TABLE 4. In vitro dissolution curve for formulation 6 in phosphate buffer pH 5.8, 100 rpm.

Min	Dissolution %
5	12,1
15	43,7
30	65,0
45	77,4
60	88,3
120	95,7
180	97,4
240	97,8
300	98,1
360	98,1

Formulation 7 (matrix tablet)

Levosimendan	1,0 mg
Methocel K 100 LV	30,0 mg
Croscarmellose sodium	0,27 mg
Avicel PH-200	100,0 mg
Stearic acid	4,0 mg

Levosimendan, Methocel K 100 LV, Croscarmellose sodium and Microcrystalline cellulose (Avicel) were mixed in a suitable mixer (Turbula or equivalent). The powder blend from step was then sieved and mixed in a suitable mixer (Turbula or equivalent). Stearic acid was then sieved and mixed with the powder blend in a suitable mixer (Turbula or equivalent). The mass was then compressed into tablets with a suitable tablet machine (punch diameter 7 mm and concavity radius 10,5 mm, hardness 60 N).

Dissolution data for the above formulation (USP XXII, phosphate buffer, pH 5.8, 100 rpm) is as follows:

TABLE 5. In vitro dissolution curve for formulation 7 in phosphate buffer pH 5.8, 100 rpm.

Min	Dissolution %
10	33,7
20	47,8
30	60,9
40	72,6
50	78,5
60	82,5
90	88,5
120	90,0
180	92,2
240	94,8
300	96,9

Formulation 8 (matrix tablet)

Levosimendan	1,0 mg
Croscarmellose sodium	0,11 mg
Akofine NF	10.0 mg
Avicel PH-200	100,0 mg

Levosimendan, Croscarmellose sodium and Microcrystalline cellulose (Avicel) were mixed in a suitable mixer (Turbula or equivalent). The powder blend from step was then sieved and mixed in a suitable mixer (Turbula or equivalent). Akofine NF (hydrogenated vegetable oil) was then sieved and mixed with the powder blend in a suitable mixer (Turbula or equivalent). The mass was then compressed into tablets with a suitable tablet machine (punch diameter 7 mm and concavity radius 10,5 mm, hardness 60 N).

Various modifications and variations can be made to the disclosed embodiments without departing from the subject of the invention as defined in the following claims.

CLAIMS

1. A controlled release composition for oral administration comprising a) a therapeutically effective amount of levosimendan and b) a drug release controlling component for providing the release of levosimendan over an extended period of time and a steady-state plasma level for metabolite (II) of less than 20 ng/ml, preferably less than 10 ng/ml.

2. A composition of claim 1 wherein the drug release controlling component allows levosimendan to be released substantially completely before the composition reaches the large intestine.

3. A composition of claim 1 or 2 wherein the drug release controlling component is hydrophilic gel forming polymer or a vegetable fat or oil or a fatty acid ester.

4. A controlled release composition for oral administration comprising a) a therapeutically effective amount of levosimendan and b) a drug release controlling component for providing the release of levosimendan over an extended period of time, wherein the total in vitro dissolution time, determined according to the USP XXII basket assembly method in phosphate buffer pH 5.8, is substantially between 1 and 4 hours for at least 90 per cent of the content of levosimendan.

5. A controlled release composition for oral administration comprising (a) a rapid release portion comprising levosimendan optionally together with at least one excipient, and (b) a controlled release portion comprising levosimendan and a drug release controlling component.

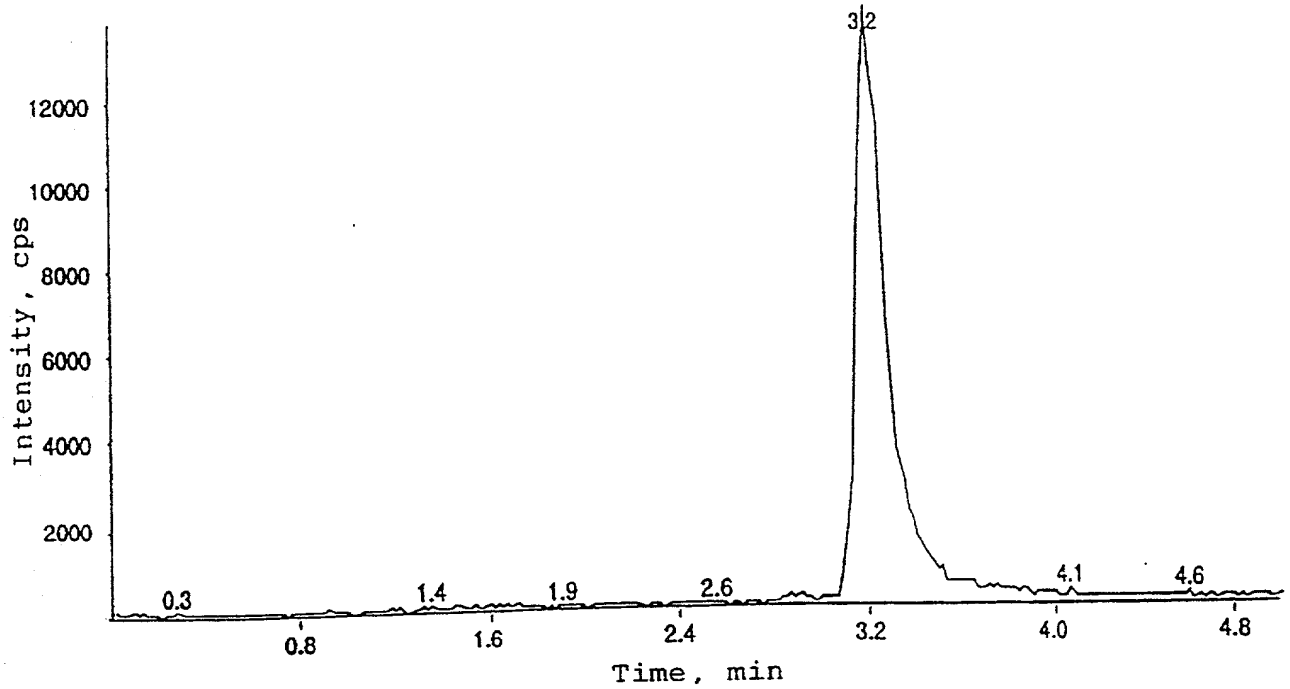
6. A composition of claim 5 comprising (a) a rapid release portion in the form of a powder comprising levosimendan together with at least one excipient, and (b) a controlled release portion in the form of granulates comprising levosimendan and a release controlling hydrophilic gel forming polymer.

7. A composition of claim 5 or 6 wherein the rapid release portion comprises levosimendan and microcrystalline cellulose.

8. A composition of claim 6 or 7 wherein the release controlling hydrophilic gel forming polymer is hydroxypropylmethyl cellulose, alginic acid or a mixture thereof.

9. A composition of any of claims 5 - 8 wherein about 25 - 75 %, preferably about 30 - 70 %, more preferably about 40 - 60 % per weight of the drug is in the controlled release portion.

10. A composition of any of claims 5 - 9 wherein the amount of the hydrophilic gel forming polymer is about 20 - 80 %, preferably about 30 - 70 %, per weight of the composition.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6000
4000
2000
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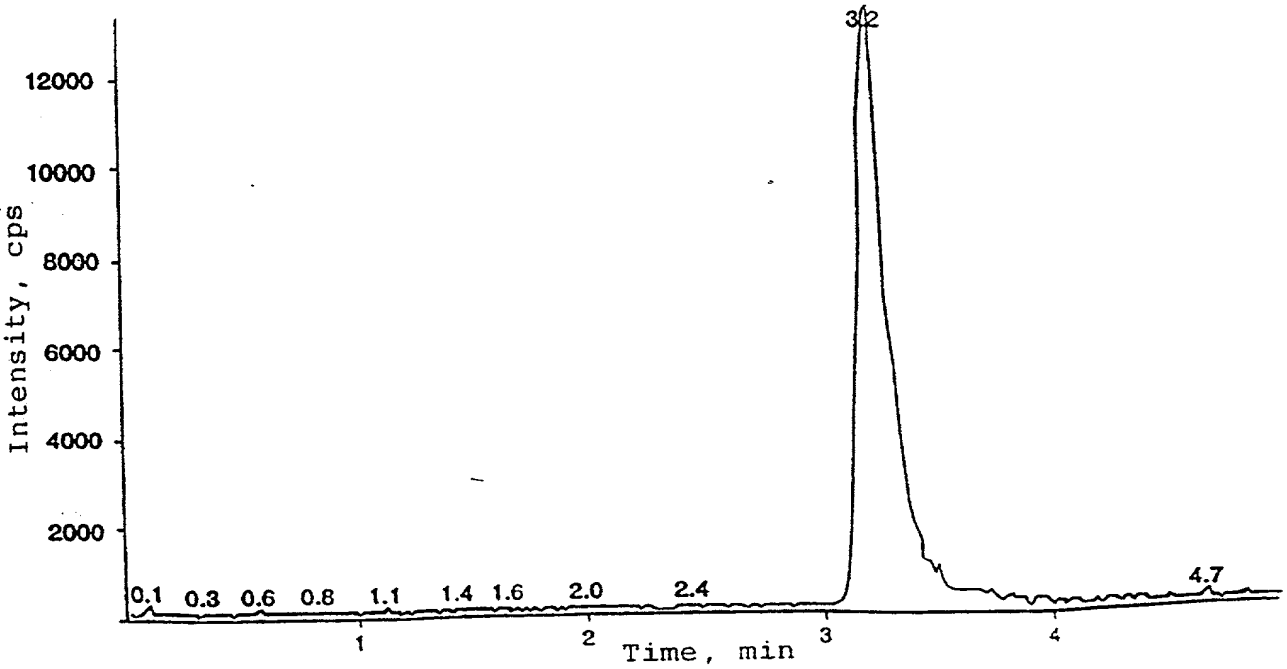
0.3
1.4
1.9
2.6
4.1
4.6
0.8
1.6
2.4
3.2
4.0
4.8
Time, min

FIG. 1


Intensity, cps
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0.3
0.6
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1.6
2.0
2.4
4.7
1
2
3
4
Time, min

FIG. 2

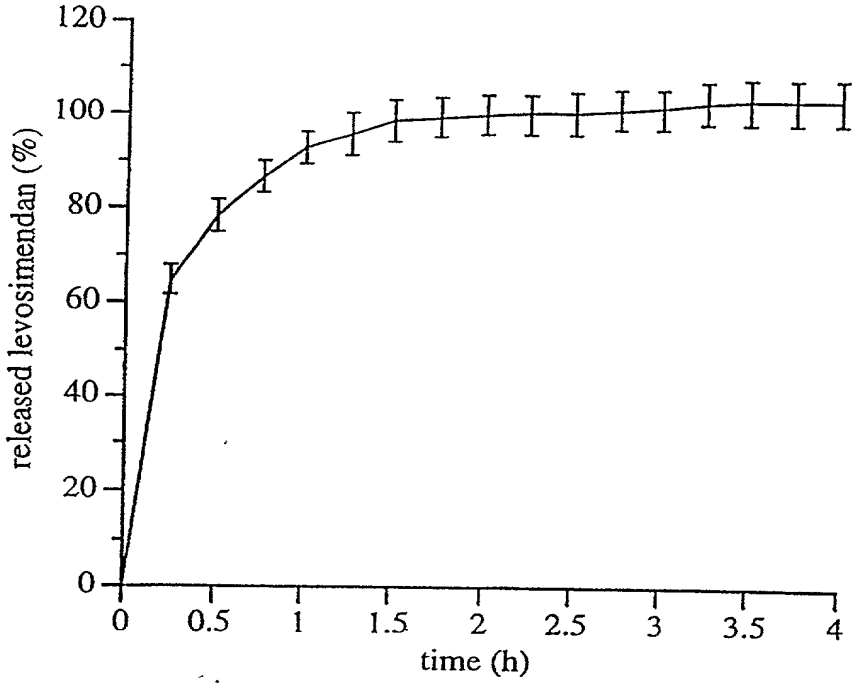
120
100
80
60
40
20
0
released levosimendan (%)
0
0.5
1
1.5
2
2.5
3
3.5
4
time (h)

FIG. 3

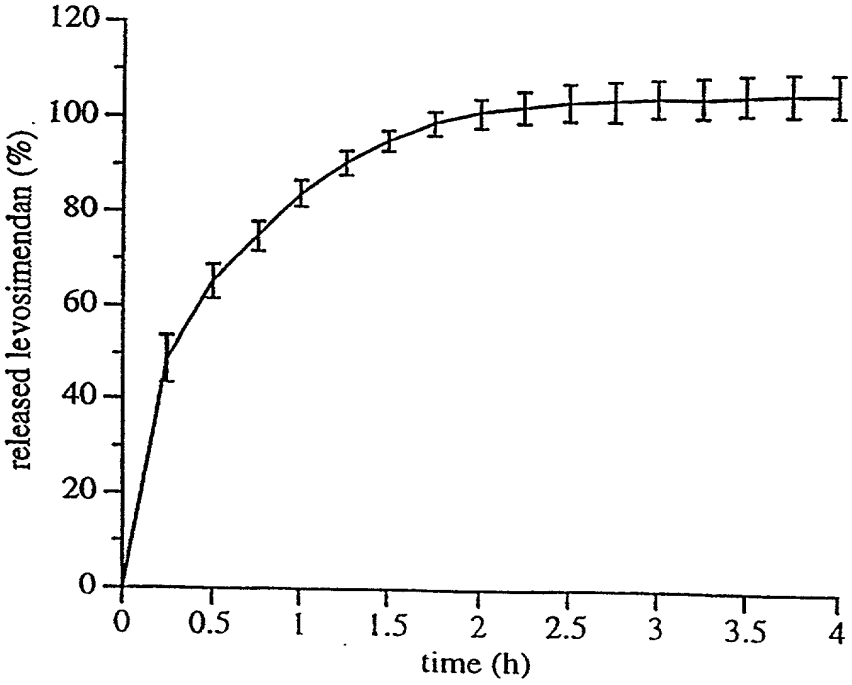
120
100
80
60
40
20
0
released levosimendan (%)
0
0.5
1
1.5
2
2.5
3
3.5
4
time (h)

FIG. 4

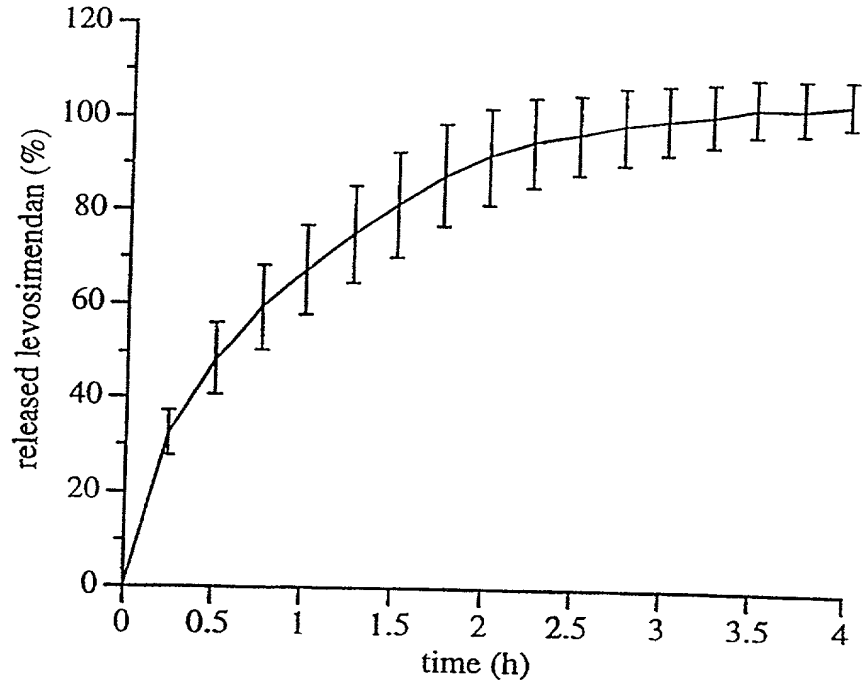
120
100
80
60
40
20
0
released levosimendan (%)
0
0.5
1
1.5
2
2.5
3
3.5
4
time (h)

FIG. 5

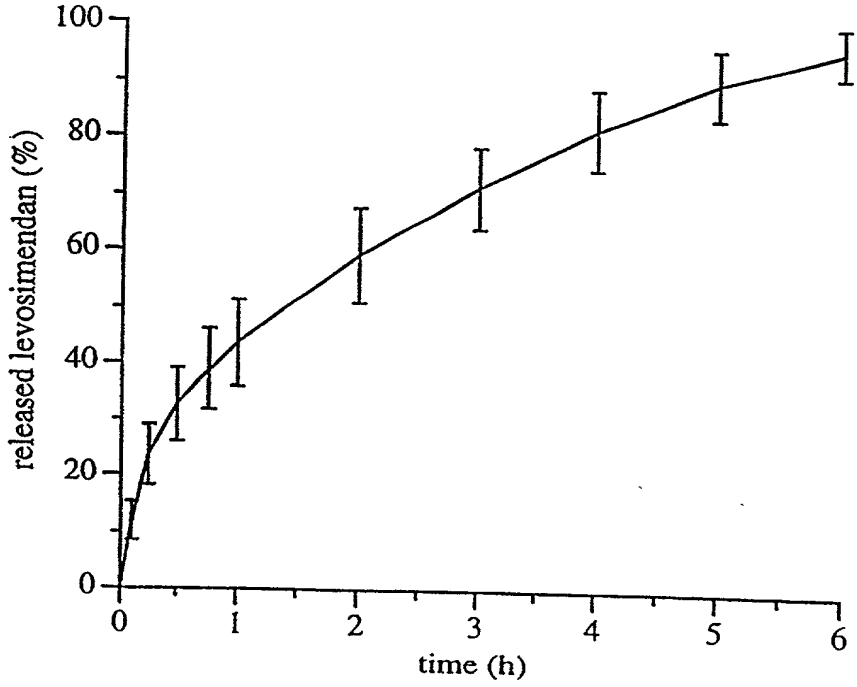
100
80
60
40
20
0
released levosimendan (%)
0
1
2
3
4
5
6
time (h)

FIG. 6

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

CONTROLLED RELEASE PERORAL COMPOSITIONS OF LEVOSIMENDAN

the specification of which:

is attached hereto; or

was filed as United States Application Serial No. **serial number** on **filing date**, and was amended on _____ (if applicable); or

was filed as PCT International Application Number PCT/FI99/00329 on April 23, 1999 and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate or § 365(a) of any PCT international application(s), designating at least one country other than the United States, listed below and have also identified below any foreign application(s) for patent or inventor's certificate, or any PCT international application(s) having a filing date before that of the application(s) of which priority is claimed:

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119
Finland	980901	April 23, 1998	☒YES ☐ NO
			☐ YES ☐ NO

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Number	Date of Filing

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT international application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

Application Number	Date of Filing	Status (Patented, Pending, Abandoned)

I hereby appoint the following attorney and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Reg. No. 22,540**, Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings IV, Reg. No. 20,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewris, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, Reg. No. 30,413; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Y. Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No. 32,095; Jean B. Fordis, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,120; James K. Hammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,824; Dirk D. Thomas, Reg. No. 32,600; Thomas W. Banks, Reg. No. 32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanho Sonu, Reg. No. 33,457; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,867; James W. Edmondson, Reg. No. 33,871; Michael R. McGurk, Reg. No. 32,045; Joann M. Neth, Reg. No. 36,363; Gerson S. Panitch, Reg. No. 33,751; Cheri M. Taylor, Reg. No. 33,216; Charles E. Van Horn, Reg. No. 40,266; and Linda A. Wadler, Reg. No. 33,218; Jeffrey A. Berkowitz, Reg. No. 36,743; Michael R. Kelly, Reg. No. 33,921; James B. Monroe, Reg. No. 33,971; Doris Johnson Hines, Reg. No. 34,629; Allen R. Jensen, Reg. No. 28,224; Lori Ann Johnson, Reg. No. 34,498; and David A. Manspeizer, Reg. No. 37,540 and Steven J. Scott, Reg. No. 43,911. Please address all correspondence to **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.**, 1300 I Street, N.W., Washington, D.C. 20005, Telephone No. (202) 408-4000.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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